

Circuit formation in the adult brain

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Abstract

Neurons in the mammalian central nervous system display an enormous capacity for circuit formation during development but not later in life. In principle, new circuits could be also formed in adult brain, but the absence of the developmental milieu and the presence of growth inhibition and hundreds of working circuits are generally viewed as unsupportive for such a process. Here, we bring together evidence from different areas of neuroscience—such as neurological disorders, adult-brain neurogenesis, innate behaviours, cell grafting, and in vivo cell reprogramming—which demonstrates robust circuit formation in adult brain. In some cases, adult-brain rewiring is ongoing and required for certain types of behaviour and memory, while other cases show significant promise for brain repair in disease models. Together, these examples highlight that the adult brain has higher capacity for structural plasticity than previously recognized. Understanding the underlying mechanisms behind this retained plasticity has the potential to advance basic knowledge regarding the molecular organization of synaptic circuits and could herald a new era of neural circuit engineering for therapeutic repair.

KEYWORDS

adult brain, adult-born neuron, brain repair, cell grafting and reprogramming, circuit formation, sprouting

1 | INTRODUCTION

1.1 | Aim and scope of this review

The field of developmental neurobiology has generated extensive knowledge regarding the wiring of complex neural circuits (Squire et al., 2012). By contrast, circuit

formation in the mammalian adult brain has not been widely considered because it is thought that axonal wiring rapidly declines after development and the adult brain cannot generally self-repair damaged circuits. In addition, the vast backdrop of developmentally established circuits makes the observation of any new circuit inherently challenging. However, technological

Abbreviations: AVPV, anteroventral periventricular; bHLH, basic helix–loop–helix; CLK, Clock; CYC, cycle; dLGN, dorsal lateral geniculate nucleus; DN1a, dorsa-anterior clock neurons; ESCs, embryonic stem cells; GCs, granule cells; iPSCs, induced pluripotent cells; LNv, ventral lateral neurons; MAG, myelin associated glycoprotein; NG2, neural/glial antigen 2-expressing; NMDA, *N*-methyl-D-aspartate; NSCs, neural stem cells; 6-OHDA, 6-hydroxydopamine; OMgp, oligodendrocyte myelin glycoprotein; PR, progesteron receptor; RTN4, Reticulon 4, Nogo; QA, quinolinic acid; SC, superior colliculus; SVZ, subventricular zone; VMHvl, ventrolateral part of the ventromedial hypothalamus.

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advances—first, intracellular labelling of neurons with dye and, more recently, rapid developments in transgenic (Navabpour et al., 2020), whole-brain imaging (Ueda et al., 2020), and cell programming technologies (Gascón et al., 2017)—now allow more thorough analysis of brain circuits. Concomitantly, accumulating evidence shows circuit formation in adult brain. This review aims to combine such pieces of evidence from different areas of neuroscience and to derive hypotheses about underlying molecular mechanisms. We focus on adult-brain circuit formation characterized by gross axonal remodelling. We do not address forms of experience- and homeostasis-dependent synapse formation and pruning and dendritic plasticity (Bennett et al., 2018; Holtmaat & Svoboda, 2009; Trincherio et al., 2017), which may alter circuit connectivity, but are not evinced by gross axon morphological changes. First, we give a brief overview of known principles of circuit formation taken from developmental neurobiology, because they provide an established framework for wiring processes. Then, we review examples of circuit formation in adult brain. And finally, we discuss key steps of adult-brain circuit formation and mechanisms that potentially support these.

1.2 | Principles of circuit formation

Developmental studies consider axon elongation, target recognition and synapse formation as key steps of circuit formation. After neurogenesis and migration, developing neurons display a remarkable capacity for axon growth. Elongating axons are guided through molecularly distinct areas and decision points, for example, crossing of midline or cell layers, until they reach their intended target (Goodman & Shatz, 1993; Kania & Klein, 2016; Polleux et al., 2007; Squire et al., 2012; Stoeckli, 2018; Tessier-Lavigne & Goodman, 1996). Molecularly, axon guidance is mediated by guidance cues—such as members of the netrin, slit, semaphorin and ephrin families—in surrounding tissue and by their receptors on the axon. [Correction added on 8 July 2022, after first online publication: ‘semaphoring’ was changed to ‘semaphorin’ in the previous sentence.] A guidance effect can be characterized as repellent or attractant. The combinations of different repellent and attractant forces are believed to be fundamental to create accurate axonal projections across the nervous system.

After reaching the final target area, the next challenge for axons is to recognize appropriate partner neurons from a potentially diverse pool of cells present in that area. Matching combinations of synaptic cell surface

receptors and adhesion molecules displayed on the axon and target neurons are hypothesized to provide a molecular code for target recognition (Sanes & Zipursky, 2020; Sperry, 1963; Südhof, 2018, 2021; Zipursky & Sanes, 2010). Although such a molecular code has not been completely clarified, this hypothesis is supported by many observations showing the importance of cadherin, leucine-rich repeat, immunoglobulin, teneurin, and latrophilin protein families in target recognition.

Circuit formation begins in the embryo and continues after birth. When circuits obtain their adult-like pattern, the developmental drive for axon growth declines. In rodents, which we mostly focus on, growth decline prominently occurs 1–4 weeks after birth (Figure 1). However, timing of the decline varies between circuits. For example, the mature arrangement of thalamocortical axons in somatosensory cortex is virtually established by 8 days after birth (López-Bendito & Molnár, 2003), whereas the density of dopaminergic fibres in the medial prefrontal cortex increases at least until 2 months after birth (Kalsbeek et al., 1988). In addition to growth decline, synaptic competition, elimination of exuberant axons, and activity-dependent refining processes contribute to the formation and maturation of neuronal circuits (Innocenti & Price, 2005; Katz & Shatz, 1996; Squire et al., 2012). The rodent brain is generally considered to be mature one month after birth, when synapse density also stabilizes at adult levels (e.g., in barrel cortex) (Micheva & Beaulieu, 1996).

In contrast, in the adult brain, axon growth has been mostly studied in the context of neuronal injury and neurological disorders. After injury, axon growth can be classified as sprouting or regeneration (Tuszynski & Steward, 2012). Sprouting generally refers to axon growth from uninjured neurons, whereas regeneration mostly refers to growth effects in neurons that experienced injury. In addition, sprouting is used to describe axon growth in models of neurological disorders (regeneration is not typically investigated in this context). Because axon regeneration has the added complication of injury signalling and scar formation, we mostly refrain from including studies on axon regeneration. However, the research of different sprouting phenotypes helped to establish characteristic features (e.g., occurrence in different cell types and formation of feedback and feedforward, and typical and atypical circuits), which also appear to be relevant for other forms of circuit formation. We discuss such features below and then other examples (Figures 1 and 2), which could be used to interrogate the principles of circuit formation in the adult brain.

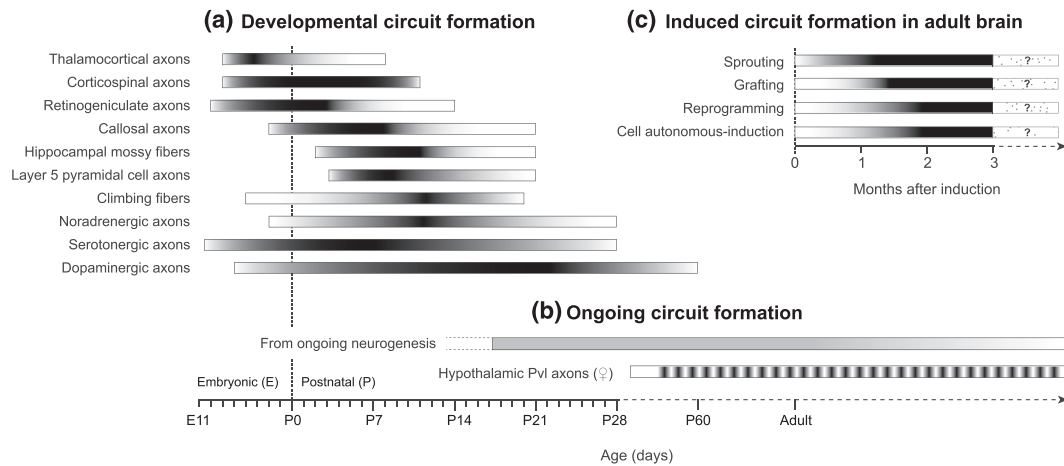


FIGURE 1 Circuit formation in developing and adult rodent brain. (a) Maturation of different axon projections in the developing brain. The mature arrangement of thalamocortical axons is virtually established by 8 days after birth (postnatal days 8, or P8) (López-Bendito & Molnár, 2003). Corticospinal axons reach the lumbar part of the spinal cord and develop collateral branching by P11 (Canty & Murphy, 2008). Retinogeniculate axons (retinal projections to LGN) are largely established by P3, but there is a significant overlap between ipsi- and contra-lateral axons, which are refined to adult-like patterns by P12–14 (natural eye opening) (Assali et al., 2014; Jaubert-Miazza et al., 2005; Muir-Robinson et al., 2002). Callosal axons are largely established by P8 and progressively refined until P21 (De León Reyes et al., 2019; Fame & MacDonald, 2011; Innocenti & Price, 2005). Hippocampal mossy fibres display a slowing growth from P10–12 and reach their final length by P21–28 (Blaabjerg & Zimmer, 2007). In somatosensory cortex, the axon length and branching of layer 5 pyramidal neurons continue to increase at least until P21 (Romand et al., 2011). Climbing fibres establish mono-innervation of cerebellar Purkinje cells by around P21 (Hashimoto & Kano, 2005; Reeber et al., 2013). Noradrenergic axon density in the neocortex reaches maximal levels between P6–16, after which it decreases to adult level by P28 (Levitt & Moore, 1979). Serotonergic axons are broadly present in multiple brain areas already at P0–7 and become largely established by P28 (Maddaloni et al., 2017). Dopaminergic axon density in the medial prefrontal cortex continues to increase until P60, after which it stabilizes at adult level (Kalsbeek et al., 1988). (b) Ongoing circuit formation in adult brain. Neurons generated from SVZ and dentate gyrus precursors continue to form circuits in adults (Denoth-Lippuner & Jessberger, 2021; Obner & Alvarez-Buylla, 2019). In female mice, hypothalamic Pvl neurons periodically extend and retract their axonal projections throughout the 5-day oestrous cycle (Inoue et al., 2019). (c) Induced circuit formation in adult brain. Sprouting, grafted, reprogrammed, and cell autonomously induced neurons can develop dense axonal projections by 14–90 days after induction. However, the end of axon growth and circuit formation in these models remains largely unknown (although see Dhar et al., 2016, in which this question was specifically investigated). Bars show the beginning and end of circuit formation. Greyscale denotes high (black) and low intensity (white) growth periods.

2 | EXAMPLES OF CIRCUIT FORMATION IN ADULT BRAIN

2.1 | Sprouting phenotypes

Sprouting is frequently observed in experimental models of stroke, traumatic injury, and epilepsy. Critically, previous observations have helped to establish that adult neurons can regain their capacity for axon growth. Because sprouting in these models has been extensively reviewed before (e.g., Carmichael et al., 2017; Jasper's *basic mechanisms of the epilepsies [internet]*, 2012), here we only highlight salient features that are of interest for this review.

First, sprouting has been observed in multiple different cell types (e.g., glutamatergic, GABAergic, serotonergic and catecholaminergic cells) and brain regions (e.g., different cortical and hippocampal regions)

(Carmichael et al., 2001; Christenson Wick et al., 2017; Dhar et al., 2016; Dougherty et al., 2020; Esclapez et al., 1999; Hawthorne et al., 2011; Jin et al., 2016; Kajstura et al., 2018; Karlócai et al., 2011; Laurberg & Zimmer, 1981; Lehmann et al., 2000; Liu et al., 2010; Luo et al., 2021; Marchionni et al., 2019; Peng et al., 2013; Perez et al., 1996; Salin et al., 1995; Schauwecker & McNeill, 1995; Shetty, 2002; Siddiqui & Joseph, 2005; Smith & Dudek, 2001; Steward, 1992; Sutula et al., 1988; Tauck & Nadler, 1985; Watt & Paden, 1991; Wenzel et al., 2000; Zhang et al., 2009) (Figure 2a and Table 1). Despite the ontogenic, functional and morphological diversity of these cell types, the fact that they all display a sprouting phenotype suggests that the capacity for further axon growth is a common feature of adult-brain neurons, regardless of their transcriptomic and epigenetic profiles.

Second, sprouting axons may remain in the local network, or they can also create long-range projections that

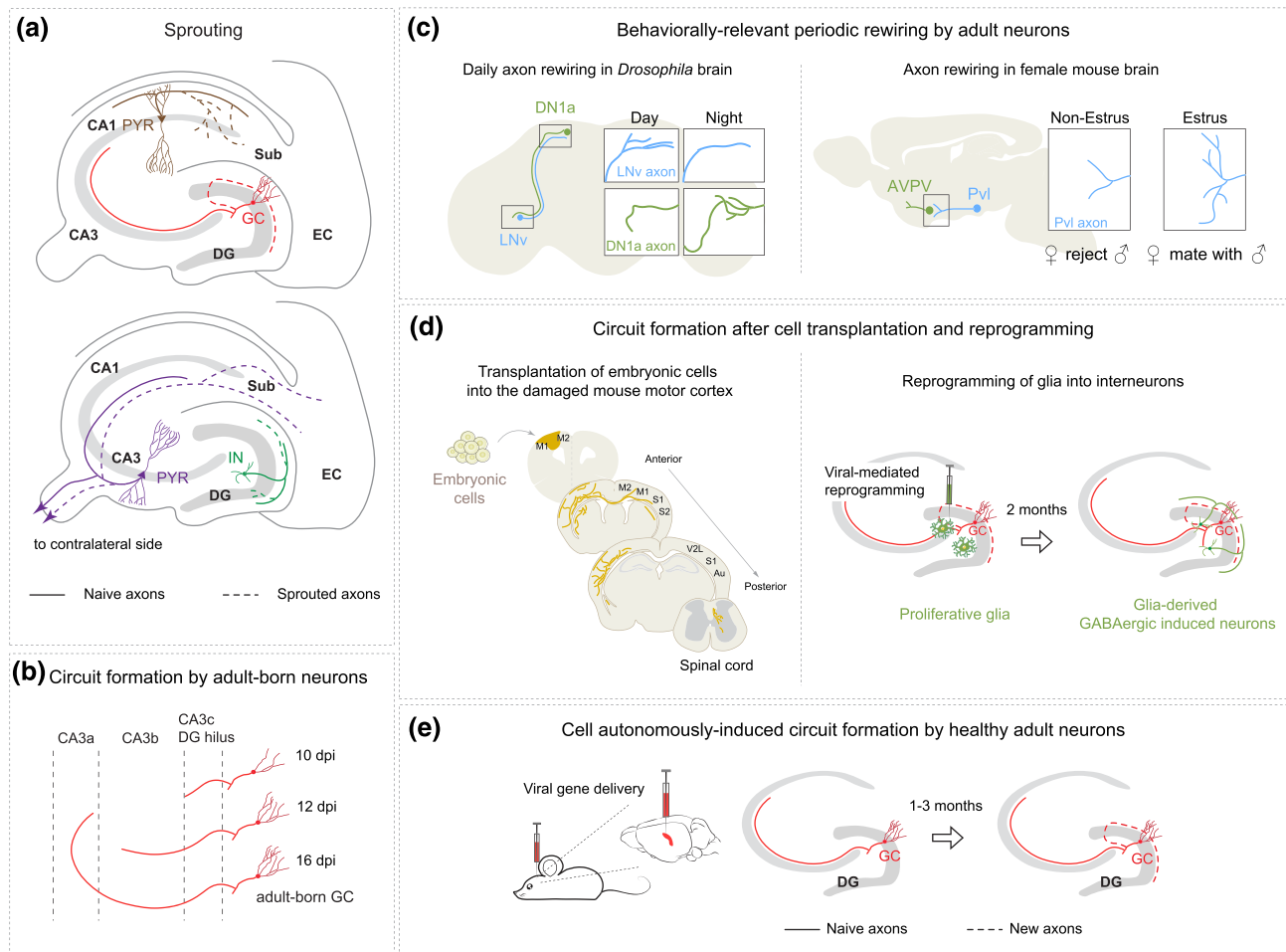


FIGURE 2 Different types of circuit formation in the adult brain. (a) Sprouting in models of neurological disorder. Upper panel shows sprouting of hippocampal granule cells, called mossy fibre sprouting, and CA1 pyramidal cells (adapted from Siddiqui & Joseph, 2005 and Esclapez et al., 1999). Lower panel shows sprouting of CA3 pyramidal cells and interneurons (adapted from Wenzel et al., 2000 and Zhang et al., 2009). (b) Circuit formation by adult-born neurons (adapted from Zhao et al., 2006). (c) Behaviourally relevant rewiring by adult neurons. Left panel shows daily axon rewiring in *Drosophila* (adapted from Song et al., 2021). Right panel shows periodic axonal rewiring in female mouse brain (adapted from Inoue et al., 2019). (d) Circuit formation after cell transplantation and reprogramming. Left panel show circuit formation after transplantation of embryonic cells into the damaged mouse motor cortex (adapted from Gaillard et al., 2007). Right panel shows circuit formation after reprogramming of glia into interneurons (adapted from Lentini et al., 2021). (e) Cell autonomously induced circuit formation by healthy adult neurons. Panel shows Id2-induced rewiring of hippocampus granule cells (adapted from Luo et al., 2021).

extend into distant brain regions. The majority of observations in this context can be classified as local sprouting (Esclapez et al., 1999; Laurberg & Zimmer, 1981; Lehmann et al., 2000; Luo et al., 2021; Marchionni et al., 2019; Peng et al., 2013; Perez et al., 1996; Smith & Dudek, 2001; Sutula et al., 1988; Tauck & Nadler, 1985; Wenzel et al., 2000; Zhang et al., 2009). Local sprouting often appears to create feedback circuits, in which the output of sprouting neurons is directed back to the same cell type, either directly (e.g., mossy fibre sprouting) or indirectly through other intermediary cell types (e.g., certain forms of CA3 pyramidal cell sprouting) (Siddiqui & Joseph, 2005). However, the occurrence of

long-range sprouting is also well supported by evidence showing inter-cortical (Liu et al., 2010), inter-hippocampal (Christenson Wick et al., 2017; Siddiqui & Joseph, 2005), and forebrain/midbrain to cortex sprouting (Dougherty et al., 2020; Hawthorne et al., 2011; Jin et al., 2016; Kajstura et al., 2018). These typically form feedforward circuits. Because sprouting has been often analysed in acute brain slice preparations, which fundamentally limit the study of long-range projections, other examples of long-range sprouting that have gone unnoticed may exist.

Third, sprouting can create typical or atypical axonal projections. Of these, typically sprouted axons overlap with

TABLE 1 List of studies demonstrating circuit formation in the adult brain

	Brain region	Cell type	Projection	References
Sprouting phenotypes	Cortex	L5 pyramidal cells	Local	Salin et al. (1995), Carmichael et al. (2001)
	Cortex	Cortical neurons	Long range to contralateral cortex	Liu et al. (2010)
	Entorhinal cortex	Entorhinal cortical neurons	Long range to hippocampal CA1	Shetty (2002)
			Long range to contralateral dentate gyrus	Steward (1992)
	Hippocampus	Granule cells	Local (mossy fibre sprouting, MFS)	Laurberg and Zimmer (1981), Tauck and Nadler (1985), Sutula et al. (1988), Wenzel et al. (2000)
				Luo et al. (2021). (<i>Many more studies show MFS.</i>)
		CA3 pyramidal cells	Long range to bilateral CA3, CA1 and subiculum, and entorhinal cortex	Siddiqui and Joseph (2005)
		CA1 pyramidal cells	Local	Perez et al. (1996), Esclapez et al. (1999), Lehmann et al. (2000), Smith and Dudek (2001), Marchionni et al. (2019)
		SST interneurons	Local	Zhang et al. (2009), Peng et al. (2013)
		CB1/CCK interneurons	Local	Karlócai et al. (2011)
		PV interneurons	Long range to contralateral hippocampus	Christenson Wick et al. (2017)
	Forebrain	Serotonergic neurons	Long range to cortex	Hawthorne et al. (2011), Jin et al. (2016), Kajstura et al. (2018)
	Midbrain	Catecholaminergic neurons	Long range to cortex	Dougherty et al. (2020)
Hypothalamus	Hypothalamic neurons	Long range to neural lobe	Watt and Paden (1991)	
Inferior olive	Inferior olivary neurons	Long range climbing fibres to cerebellar Purkinje cells	Dhar et al. (2016)	
Ongoing circuit formation by adult-born neurons	Hippocampus	Adult-born granule cells	Long range to hippocampal CA3	Markakis and Gage (1999), Zhao et al. (2006), Faulkner et al. (2008), Sun et al. (2013), Toni et al. (2008), Restivo et al. (2015), Temprana et al. (2015), Drew et al. (2016), Trincherro et al. (2019), Briones et al. (2021)
	Olfactory bulb	Interneurons	Local	

(Continues)

TABLE 1 (Continued)

	Brain region	Cell type	Projection	References
				Brill et al. (2009), Galliano et al. (2018)
	Striatum	Interneurons	Local	Ernst et al. (2014)
Behaviourally relevant circuit rewiring by adult neurons	Protocerebrum and accessory medulla	LNV and DN1a neurons	Local	Fernández et al. (2008), Gorostiza et al. (2014), Petsakou et al. (2015), Song et al. (2021)
	Hypothalamus	PR + VMHvl cells	Local	Inoue et al. (2019)
Circuit formation after stem cell transplantation and cell reprogramming	Spinal cord	Grafted stem cells	Local and long range to cortex, olfactory bulb, cerebellum	Lu et al. (2012), Lu et al. (2014), Sharp et al. (2014)
	Cortex	Grafted embryonic or stem cells	Local and long range to ipsi- and contra-lateral cortex; depending on the study, also to thalamus, spinal cord and other areas	Gaillard et al. (2007), Steinbeck et al. (2012), Tornero et al. (2013), Falkner et al. (2016), Tornero et al. (2017), Palma-Tartosa et al. (2020)
	Hippocampus	Grafted stem cells	Local and long range to contralateral hippocampus	Steinbeck et al. (2012)
	Substantia nigra	Grafted embryonic cells	Long range to striatum, nucleus accumbens, basal ganglia, thalamus, and cortex	Gaillard et al. (2009); Thompson et al. (2009)
	Striatum	Grafted stem cells	Local and long range to prefrontal cortex, globus pallidus, substantia nigra, ventromedial thalamus, subthalamic nucleus	Steinbeck et al. (2015), Grealish et al. (2015), Kirkeby et al. (2017), Cardoso et al. (2018), Adler et al. (2019), Besusso et al. (2020)
	Striatum	Neurons reprogrammed from NG2 glia	Local	Torper et al. (2015)
	Substantia nigra	DA neurons reprogrammed from astrocytes	Long range to striatum	Qian et al. (2020)
	Hippocampus	Interneurons reprogrammed from glia	Local	Lentini et al. (2021)
	Cell autonomously induced wiring in adult neurons	Hippocampus	Granule cells	Local

the developmentally established axonal profile of the neuron (Christenson Wick et al., 2017; Dougherty et al., 2020; Hawthorne et al., 2011; Jin et al., 2016; Kajstura et al., 2018; Liu et al., 2010; Salin et al., 1995; Smith & Dudek, 2001; Watt & Paden, 1991; Zhang et al., 2009). By contrast, atypically sprouted axons deviate from such developmentally established profiles and create projections

not seen in naive animals (Carmichael et al., 2001; Dhar et al., 2016; Laurberg & Zimmer, 1981; Lehmann et al., 2000; Luo et al., 2021; Peng et al., 2013; Shetty, 2002; Tauck & Nadler, 1985; Wenzel et al., 2000). Observations describing both in the same cell type (Esclapez et al., 1999; Marchionni et al., 2019; Perez et al., 1996; Siddiqui & Joseph, 2005; Steward, 1992) suggest that sprouting of

atypical or typical projections does not necessarily exclude the other, and may be present at the same time. Independently of this, examples for typical and atypical sprouting reveal target-region specificity, indicating that sprouting is often a spatially guided process.

Fourth, sprouting axons can form functional synapses. Several of the above studies further tested their sprouting phenotypes to see if circuit formation was completed after axon elongation. Using electron microscopy (Karlócai et al., 2011; Laurberg & Zimmer, 1981; Luo et al., 2021; Peng et al., 2013; Sutula et al., 1988; Wenzel et al., 2000), electrophysiology (Jin et al., 2016; Luo et al., 2021; Peng et al., 2013; Smith & Dudek, 2001; Tauck & Nadler, 1985), transneuronal retrograde labelling (Siddiqui & Joseph, 2005), and behaviour-level readouts (Jin et al., 2016; Liu et al., 2010; Luo et al., 2021), studies show evidence for synapse formation and/or synaptic transmission, supporting that sprouting creates functional circuits.

Finally, sprouting may occur rather rapidly, that is, within days. Currently, only limited information is available on the temporal development of sprouting because the time point at which they were characterized—frequently several weeks or months after induction—was often dictated by other research priorities, for example, study of seizures or motor recovery. Nonetheless, sprouting may start as early as 2–3 days after induction (Luo et al., 2021). The time required for maximal sprouting may depend on the cell type, pathology, and/or model, and remains undetermined in most studies. However, at least in one disease model, in vivo imaging of lesion-induced sprouting revealed that while sprouting lasted over months, most innervations emerged 3–4 weeks after lesion (Dhar et al., 2016).

2.2 | Ongoing circuit formation by adult-born neurons

In addition to sprouting by mature neurons, adult-born neurons have a clear capacity for wiring in healthy adult circuits. In contrast to sprouting, which requires some type of pathological state or induction, circuit formation by adult-born neurons follows genetically defined programs and is usually not considered sprouting. Major sites of adult neurogenesis include the subventricular zone (SVZ) of the lateral ventricles and hippocampal dentate gyrus. Neuroblasts from the SVZ migrate mainly to olfactory bulb in rodents (Bonzano et al., 2016; Brill et al., 2009; Oberner & Alvarez-Buylla, 2019), but to striatum in humans (Bergmann et al., 2012; Ernst et al., 2014), highlighting a species difference. SVZ-derived cells may differentiate into GABAergic, dopaminergic and glutamatergic neurons (Bonzano et al., 2016; Brill et al., 2009; Oberner & Alvarez-

Buylla, 2019), some of which remain axon-less (Galliano et al., 2018). By contrast, neurons born in dentate gyrus remain local and differentiate exclusively into granule cells (GCs) (Gonçalves et al., 2016). Independent of their neurogenic origin, adult-born neurons need to integrate into already established circuits. This process involves formation of dendrites and input synapses (out of scope for this review), as well as axons and output synapses.

These processes have been best-characterized in adult-born GCs (Denoth-Lippuner & Jessberger, 2021; Ge et al., 2008; Jahn & Bergami, 2018; Mongiat & Schinder, 2011; Song et al., 2012; Vivar & van Praag, 2013; Zhao et al., 2006) (Figure 2b). Identically to developmentally born GCs, adult-born GCs send axonal projections to the hippocampal CA3 area (Faulkner et al., 2008; Markakis & Gage, 1999; Sun et al., 2013; Zhao et al., 2006) and form synapses with dentate, hilar and CA3 interneurons, hilar mossy cells, and CA3 pyramidal cells (Briones et al., 2021; Drew et al., 2016; Restivo et al., 2015; Temprana et al., 2015; Toni et al., 2008; Trincherro et al., 2019). Thus, circuit formation by adult-born GCs is highly target-specific. In CA3, which is at least 0.5–1 mm away from GC layer, first axons appear 10 days after cell birth (Zhao et al., 2006) and only ~7 days after growing axons become visible in adult-born GCs (Zuccaro et al., 2014), which suggests an axonal elongation speed of ~0.1 mm/day. While adult-born GCs establish their initial synaptic contacts with CA3 pyramidal cells 14 days after cell birth (Faulkner et al., 2008), they continue to mature over at least 2 months, after which their axonal and synaptic structures become virtually indistinguishable from other GCs (Faulkner et al., 2008; Zhao et al., 2006).

After circuit integration, adult-born neurons support a variety behaviourally relevant computations. In dentate gyrus, they are thought to control pattern separation (differentiation of neuronal activity representing similar experiences), one principal function performed by this brain region (Nakashiba et al., 2012). In olfactory bulb, they participate in odour discrimination, associative learning, and memory (Gheusi et al., 2013; Grelat et al., 2018; Li et al., 2018; Malvaut & Saghatelian, 2016). In order to participate in these specialized computational tasks, it is crucial that the integration process of adult-born neurons is precisely controlled. However, mechanisms in adult brain such as axon guidance and target cell specification remain poorly understood.

2.3 | Behaviourally relevant, periodic circuit rewiring by adult neurons

Further evidence from fly (*Drosophila melanogaster*) and mouse studies suggests that adult-born neurons are not

the only cells that form circuits in the healthy adult brain. Behaviourally relevant circuit rewiring has been reported in both of these species, where axonal outgrowth and retraction are governed by daily or hormonal cycles.

In fly, subpopulations of ventral lateral neurons (LNv) (Fernández et al., 2008; Gorostiza et al., 2014; Petsakou et al., 2015) and dorsa-anterior clock neurons (DN1a) (Song et al., 2021) display daily periodic axonal and synaptic connectivity remodelling (Figure 2c, left panel). These cell types are interconnected and form a reciprocal inhibitory circuit. The daily schedules of their axonal remodelling, however, are in anti-phase: LNv neurons have larger axon area during daytime than nighttime, whereas axon length of DN1a neurons is shorter during daytime than night-time. Mechanistically, both processes require Rho1 (RhoA in mammals) (Petsakou et al., 2015; Song et al., 2021), as shown by cell type-specific Rho1 overexpression and depletion, which decreased and increased their axonal areas, respectively (Song et al., 2021). Rho1 activation corresponds with myosin phosphorylation and mediates axon retraction (Petsakou et al., 2015). As a link to circadian regulation, Rho1 activity itself is controlled by clock-regulated transcription of the Rho1 GEF *Pura* (Petsakou et al., 2015). Thus, rewiring by these adult neurons could be explained on an exclusively cell-autonomous basis and by activation or deactivation of a single effector, namely, Rho1. Behaviourally, dynamic reorganization of this circuit facilitates locomotive startle response to light during night-time, when light is unexpected, and its suppression during daytime, when light is omnipresent (Song et al., 2021).

In adult mouse, axons of a hypothalamic cell type undergo large-scale extension and withdrawal, and correlated with this, cells periodically connect and disconnect from their postsynaptic targets (Inoue et al., 2019) (Figure 2c, right panel). Specifically, projections of progesterone receptor-expressing neurons in the ventrolateral part of the ventromedial hypothalamus (PR + VMHvl neurons, or Pvl neurons for short) to the anteroventral periventricular (AVPV) nucleus change across the 5-day female mouse oestrous cycle. During oestrus, there are ~3 times more termini and functional connections than during non-oestrus (Inoue et al., 2019). Although this projection also exists in males, the cyclic rewiring is dependent on oestrogen signalling (could be also induced by delivery of ovarian sex hormones) and is specific to females. Intriguingly, while Pvl neurons project to multiple other areas (such as preoptic hypothalamus and periaqueductal grey), only AVPV projections, but not others, display periodic rewiring. Further experiments revealed relevance for sexual behaviour (Inoue et al., 2019). Tested

during oestrus when axons are extended, optogenetic inhibition of Pvl termini in AVPV (to mimic functional disconnection) inhibited female sexual behaviour and increased rejection of males. In this manner, this periodic rewiring controls output of an otherwise hard-wired circuit for innate behaviour.

Thus far, molecular mechanisms of axon elongation, synapse formation, and retraction by Pvl neurons have not been investigated. Likewise, the question of whether in addition to these examples other adult neurons also use circuit rewiring to support behaviourally relevant functions remains open.

2.4 | Circuit formation after cell transplantation and reprogramming

Advances in in vivo cellular engineering have also provided insights into circuit formation in adult brain. In this area, embryonic or stem cell transplantation (also referred to as grafting), and molecular re-differentiation of existing cells are used as key approaches to generate new neurons (Björklund & Parmar, 2020; Gascón et al., 2017; Henriques et al., 2019). In rodents, newly engineered neurons can be now selectively visualized with fluorescent proteins, which has helped to reveal their striking capacity for circuit formation throughout the central nervous system. Here, we review such evidence and highlight functional consequences when information is available.

In injured spinal cord, grafted neural stem cells (NSCs) and progenitors, and cultured human embryonic stem cells (ESCs) displayed rapid axon growth only 2 days later, which continued at a rate of 1–2 mm/day (Lu et al., 2012). New synapses and myelination could be observed 7 weeks after grafting, and injury-induced motor deficits significantly improved 3–6 weeks after grafting (Lu et al., 2012). Later, an independent replication study confirmed the extensive axon growth phenotype (Sharp et al., 2014). However, motor recovery could not be confirmed, which was possibly due to lack of functional relay formation across the graft (see Sharp et al., 2014, for detailed methodological discussion). In a separate study, the first group used human induced pluripotent cells (iPSCs; derived from a healthy 86-year-old male) for grafting, which revealed even more pronounced axon growth after 3 months (Lu et al., 2014). In addition to spinal cord, axons of spinally transplanted cells were observable as distantly as in the cortex, olfactory bulb, and cerebellum. However, grafts divided into rostral and caudal compartments, between which axons did not travel, and there was no motor improvement either.

In cortical areas, homotopic transplantation of embryonic motor cortical cells into damaged adult motor cortex lead to long-range axon growth (Gaillard et al., 2007) (Figure 2d, left panel). Two months after transplantation, grafted neurons projected to appropriate ipsi- and contralateral cortical and subcortical target areas, including thalamus and spinal cord. Further, graft cell axons appeared to be myelinated, and formed synaptic contacts with cortical, striatal and thalamic host neurons. In another study, embryonic neocortical cells were transplanted into an area of visual cortex, where layer 2/3 neurons were previously selectively ablated (Falkner et al., 2016). Using chronic *in vivo* two-photon imaging, the authors showed that grafted cells developed into pyramidal cells and displayed largely stable pre- and post-synaptic structures 8–10 weeks after grafting. The cells projected to mostly appropriate areas (e.g., ipsi- and contra-lateral visual cortex) and received appropriate synaptic afferents (most prominently from dorsal lateral geniculate nucleus, dLGN, and other higher-order cortical areas). Four to fifteen weeks after grafting, most cells exhibited stimulus-evoked responses, about half of which displayed tuning-properties typical for layer 2/3 pyramidal neurons (Falkner et al., 2016).

Similar to embryonic cells, the grafting of human ESC-derived long-term self-renewing neuroepithelial stem cells into primary motor cortex also resulted in long-range connections into the cervical spinal cord and contralateral cortex within 6 weeks, with a speed of up to 1 mm/week (Steinbeck et al., 2012). Grafts placed in the dentate gyrus made projections to both ipsilateral and contralateral hippocampi, and formed synaptic connections with host cells (Steinbeck et al., 2012). In other studies, human iPSC-derived cortical neurons were transplanted into stroke-injured cortex of rat, and established monosynaptic wiring with contralateral cortical cells (Palma-Tortosa et al., 2020; Tornero et al., 2013), displayed myelinated axons (Palma-Tortosa et al., 2020), and received synaptic contacts from host cortical and thalamic neurons (Tornero et al., 2017). With regard to functional consequences, Tornero et al. (2013) found significant recovery from stroke-induced motor deficits 2 months after grafting, Tornero et al. (2017) found synaptic recruitment of grafted cells by thalamic efferents and sensory stimuli 2–3 months after grafting, and Palma-Tortosa et al. (2020) showed that although grafted cells could not reverse stroke-induced sensorimotor deficits, they regulated motor function similar to endogenous cortical neurons 6 months after grafting.

In lesioned substantia nigra, homotopic transplantation of embryonic mesencephalic cells helped to reconstitute the dopaminergic nigrostriatal pathway after 6-OHDA-induced lesion (Gaillard et al., 2009; Thompson

et al., 2009), which is a frequently used model in Parkinson's research. Growing axons became visible and exited the graft 3 and 5 days after grafting, respectively (Gaillard et al., 2009). Grafted cells developed either into mostly dopamine neurons (Thompson et al., 2009) or diverse neuronal populations (i.e., dopaminergic, serotonergic, GABAergic, and cholinergic cells) (Gaillard et al., 2009), of which only dopaminergic fibres appeared to project outside the graft (Gaillard et al., 2009). After a week, growing axons reached the striatum and multiple other brain areas (Gaillard et al., 2009). Six weeks after grafting, axons were present in striatum, nucleus accumbens, bed nucleus of the stria terminalis, reaching as far as the frontal cortex and olfactory tubercle, ~6–7 mm from the graft (Thompson et al., 2009). Two to three months after grafting, axons were broadly present in striatum, nucleus accumbens, globus pallidus, caudate putamen, thalamus, and motor cortex (Gaillard et al., 2009). Four months after grafting, axons further expanded to cover larger areas in striatum and forebrain (Thompson et al., 2009). Despite the diversity of projections, the highest density of axons was seen to target the striatum in both studies (Gaillard et al., 2009; Thompson et al., 2009). Furthermore, lesion-induced motor deficits significantly recovered 2–3 months (Gaillard et al., 2009) or 4 months (Thompson et al., 2009) after grafting. The survival of transplanted cells and extent of axon growth appeared to depend on the presence or absence of developmentally grown dopaminergic projections, because in non-lesioned mice axon outgrowth was less dense after grafting (Thompson et al., 2009). These observations suggested that axon growth and target-region specification was regulated by specific interactions between grafted cells and host environment.

Cells grafted into striatum also produced remarkable axon growth. Using differentiated human ESCs in the context of Parkinson's disease (6-OHDA model), graft-to-host and host-to-graft connectivity were observed 6 months after transplantation (Grealish et al., 2015). Grafted cells received monosynaptic connections from host cells in striatum, cortex, thalamus, amygdala, dorsal raphe nucleus, and substantia nigra. Efferent mapping revealed that the grafted cells produced dense innervation and synaptic contacts not only with surrounding striatal but also with distal targets including prefrontal cortical neurons up to 5 mm away (Grealish et al., 2015; see also Adler et al., 2019; Cardoso et al., 2018; Kirkeby et al., 2017). Functional synaptic transmission to host cells after striatal grafting has been also confirmed (Steinbeck et al., 2015). Consistent with the ability of grafted cells to undergo circuit formation, differentiated ESCs implanted in a Huntington's disease (QA lesion) model received excitatory inputs and exhibited

long-range fibre axon within striatum, and into globus pallidus, substantia nigra, ventromedial thalamus, and subthalamic nucleus (Besusso et al., 2020). All studies that looked into functional consequences found significant recovery from lesion-induced motor deficits 16–24 weeks after grafting (Besusso et al., 2020; Cardoso et al., 2018; Kirkeby et al., 2017; Steinbeck et al., 2015).

Similar to transplantation, *in vivo* conversion of existing non-neuronal cells into neuronal types also resulted in significant axon growth and target region-specific projections. In striatum, neurons converted from neural/glial antigen 2-expressing (NG2) glia showed integration within the local circuitry (Torper et al., 2015). In substantia nigra, dopaminergic neurons converted from astrocytes reconstructed the nigrostriatal circuit in a model of Parkinson's disease (Qian et al., 2020). In this model, 6-OHDA lesion-induced motor deficits were reversed to normal levels 3 months after cell conversion. Of note, that cell conversion technique used in this study was later tested by other groups in the striatum, but there astrocyte-to-neuron cell conversion could not be replicated (Chen et al., 2022; Wang, Serrano, et al., 2021). Thus, the question remains what region-specific differences, other neurogenic cell types (if not astrocytes) or mechanisms could have contributed to the axon growth phenotypes and motor recovery seen in the original study. Finally, in hippocampus, conversion of reactive glia into inhibitory interneurons led to axon growth and synapse formation, and reduced chronic seizure activity 6–8 weeks after cell conversion in a mouse model of temporal lobe epilepsy (Lentini et al., 2021) (Figure 2d, right panel). Given the rapid rate at which reprogramming techniques develop, outstanding questions will be hopefully soon clarified, and it is likely that several further examples will emerge in the near future.

Taken together, these examples provide evidence for long-range circuit formation in adult brain. Several studies demonstrated functional synaptic transmission between new and host neurons, and/or that new circuits can restore function in pathological context. While the long-term stability of newly engineered circuits remains largely unexplored, the above results indicate that circuit maturation is completed within a few weeks or months. Given that these examples frequently displayed target region-specificity, growing axons likely utilized available guidance cues, the identity of which is yet unknown. Of note, similarly to adult-born neurons, these wiring effects may take place under a hybrid combination of developmental and adult conditions, rather than only adult, because grafted and reprogrammed cells are inherently immature in the beginning. Because no additional manipulations were required to promote wiring, these observations also suggest that newly generated neurons

automatically proceed with circuit formation. While some of the studies have looked into inhibitory factors that may interfere with axon growth (Lu et al., 2012; Steinbeck et al., 2012), cell-intrinsic mechanisms that counteract growth inhibition remain elusive. Progress in these areas will be likely facilitated by the investigation of grafting into healthy brain, which may reveal differences from those in disease models (e.g., Grade et al., 2021; Steinbeck et al., 2012; Thompson et al., 2009).

2.5 | Cell autonomously induced circuit formation by healthy adult neurons

The examples above highlight that the adult brain is capable of building new circuits, and also that little is understood of the underlying molecular mechanisms. Thus far, questions related to adult wiring mechanisms have been mostly studied in injury models, where one of the key aims is to identify molecules that can facilitate circuit repair (Fink et al., 2017; Kauer et al., 2021; Mahar & Cavalli, 2018). The induction of axon growth is typically not studied in the absence of injury. While it is important to consider injury-related signalling, studying axon growth in healthy neurons provides a simplified context and unperturbed setting to identify cell-intrinsic wiring mechanisms, without the complication of other pathological signals not necessarily related to wiring. In this part, we focus on a study from our own laboratory (Luo et al., 2021) (Figure 2e) and discuss its results in the context of others.

Our motivation behind this study was to identify cell-intrinsic mechanisms underlying the epilepsy-associated hippocampal mossy fibre sprouting by adult GCs. Apart from human pathology, mossy fibre sprouting has been studied using different experimental models of epilepsy in rodents (*Jasper's basic mechanisms of the epilepsies [internet]*, 2012). In these models, in addition to mossy fibre sprouting, cell dispersion and death, and eventually seizures may develop. For a long time, sprouting mechanisms remained elusive and the question of whether mossy fibre sprouting contributed to seizures and memory deficits was debated. Using single-cell RNA sequencing, we investigated transcriptomic changes in GCs after intrahippocampal kainic acid injection-induced sprouting and searched for its mechanisms (Luo et al., 2021). In this study, we showed that sole overexpression of the single gene *Id2*, which became highly expressed after sprouting, had the remarkable capacity to induce mossy fibre sprouting in healthy adult GCs of mice and rats. The new synapses formed on other GC dendrites, had an abundant supply of synaptic vesicles, and transmitted physiologically typical signals.

Functionally, Id2 is a transcriptional regulator that inhibits the activity of mainly basic helix–loop–helix (bHLH) (Lasorella et al., 2006) but also other transcription factors (Roschger & Cabrele, 2017). This suggests that ongoing transcriptional programs actively suppressed sprouting in GCs until Id2 removed this suppression.

In contrast to human and experimental epilepsy, Id2-induced mossy fibre sprouting did not induce electrographic seizures or severe memory deficits (Luo et al., 2021). Mice displayed normal hippocampal oscillations during freely moving behaviour. However, type-2 dentate spikes, previously associated with the transfer of global navigation cues from entorhinal cortex to hippocampus, were selectively lost. Further analyses confirmed that while mice with the Id2-induced circuit still solved spatial problems just as well as controls, they relied on local rather than global navigation cues. Likely, epileptic seizures and severe memory deficits require other changes in the circuit, which are not induced by Id2. In this manner, cell-autonomous activation of wiring helped to separately analyse consequences of mossy fibre sprouting and its contribution to the disorder. Furthermore, while other studies have previously suggested the involvement of Id2 in axon growth in cultured, developing and/or injured neurons (Huang et al., 2019, 2021; Ko et al., 2016; Lasorella et al., 2006; Yu et al., 2011), the study of Id2 in context of mossy fibre sprouting revealed that activation of this molecule relieves ongoing transcriptional suppression of wiring and induces target-specific rewiring in healthy adult circuits (Luo et al., 2021).

Cell autonomously induced wiring in healthy neurons thus represents a powerful approach to investigate and explore the potential of circuit formation in the adult nervous system. Many questions have opened themselves for future studies, for example, if wiring could be activated in neuron types other than GCs.

3 | KEY STEPS OF ADULT-BRAIN CIRCUIT FORMATION

Examples above thus highlight the formation of new circuits in the adult brain. These involve axonal elongation, target specification, and synapse formation, which are also key steps during development. The developmental process is orchestrated by a multitude of molecules that together are thought to represent a code for connectivity. Adult neurons feasibly utilize the same code. However, neuronal age, epigenetic and transcriptomic states, and already established circuit environments likely impose restrictions on how such a code may be executed.

3.1 | Transcriptional control of adult-brain wiring

Studies on development and regeneration have proposed several transcription factors in promoting axon growth and facilitating axon guidance (e.g., members of the CREB, HDAC, KLF, SMAD, STAT, SOX, and bHLH families) (Mahar & Cavalli, 2018; Moore & Goldberg, 2011; Polleux et al., 2007). Although wiring programs are not activated under typical neurophysiological states in most adult neurons, it is increasingly evident that targeted manipulation of transcription factors and regulators can reactivate wiring in adults and that bHLH proteins may be important for this.

bHLH transcription factors and regulators (e.g., members of the ASCL, ID, NEUROD, NPAS, MYC and TCF families) have been recognized as essential regulators of neural cell fate determination during development (Baker & Brown, 2018; Dennis et al., 2019; Imayoshi & Kageyama, 2014; Squire et al., 2012). They drive cells to differentiated neuronal states and characteristic axonal structures. Evidence showing that ectopic expression of the bHLH transcriptional regulator Id2 can induce axon growth in developing, regenerating, and adult neurons, further suggested this family to be involved specifically in wiring (Huang et al., 2019, 2021; Ko et al., 2016; Lasorella et al., 2006; Luo et al., 2021; Yu et al., 2011). Additional observations support this. (i) The expression of multiple bHLH-encoding genes changes in models of injury, stroke, and epilepsy, in which sprouting is also known to occur (Aronica et al., 2001; Avansini et al., 2018; Elliott et al., 2001; Kabos et al., 2002; Kawai et al., 2005; Lösing et al., 2017; Luo et al., 2021; Wang et al., 2014; Zhang et al., 2014), and bHLH members have been also shown to facilitate axon regeneration and/or circuit repair (Belin et al., 2015; Buffo et al., 2005; Cho et al., 2015; Huang et al., 2021; Ko et al., 2016; Lai et al., 2020; Li et al., 2020; Ma et al., 2019; Wang et al., 2014; Williams et al., 2015; Yan et al., 2018; Zhang et al., 2014) (Table 2). (ii) Several bHLH factors have been implicated in the control of adult neurogenesis and maturation of adult-born neurons (Brill et al., 2009; Carrica et al., 2019; Gao et al., 2009; Havrda et al., 2008; Jessberger et al., 2008; Matsuda et al., 2012; Ozen et al., 2007; Shariq et al., 2021; Sueda et al., 2019) (Table 2). (iii) RhoA (Rho1 in *Drosophila*), a key intracellular regulator of axon growth, is potentially controlled by multiple bHLH transcription factors: Clock, Neurog2 and Ascl1. In *Drosophila*, Clock is presumed to control the expression of Rho1 GEF Pura, which regulates Rho1 activity (Petsakou et al., 2015), and knock-out of Clock disturbed the circadian regulation-dependent startle response that correlates with periodic rewiring (Song

TABLE 2 bHLH factors associated with models of adult-brain circuit formation

Gene name	Observation	References	Related genes/molecules based on UniProt and/or STRINGDB
Ascl1 (bHLHa46)	Upregulated after seizures; facilitates axon regeneration.	Elliott et al. (2001) Williams et al. (2015)	<u>TCF3</u> , <u>TCF12</u> , <u>TCF4</u> , <u>NEUROG2</u> , <u>HES1</u> , <u>ID1</u> , <u>ID2</u> , <u>MEF2A</u>
Hes1 (bHLHb39)	Downregulated after spinal cord hemisection; upregulated after stroke and facilitates regeneration; controls adult neurogenesis after injury.	Kabos et al. (2002) Li et al. (2020) Zhang et al. (2014) Yan et al. (2018)	SIRT1, TLE1, HES6, FA complex (FANCE, FANCG, FANCA, FNACF, FANCL, FAAP100), RBPJ, NOTCH2
Hes5 (bHLHb38)	Downregulated after seizures, spinal cord hemisection and stroke.	Elliott et al. (2001), Kabos et al. (2002), Kawai et al. (2005)	Groucho/TLE family, SOX2, SIRT1, HELT, CHD7, RPB1, NOTCH2, HES1
HIF1a (bHLHe78)	Facilitates axon regeneration.	Cho et al. (2015)	ARNT, COPPS5, SENP1, HIF3A, FOXA2, CREBBP, EP300, VHL, EGLN1
Id2 (bHLHb26)	Upregulated after seizures and/or sprouting; facilitates axon regeneration.	Aronica et al. (2001), Elliott et al. (2001), Luo et al. (2021), Huang et al. (2021), Ko et al. (2016)	<u>OLIG1</u> , <u>OLIG2</u> , <u>PPIA</u> , <u>TFE2</u> , <u>TCF3</u> , <u>TCF4</u> , <u>TCF12</u> , <u>MYOD1</u>
Myc (bHLHe39)	Facilitates axon regeneration.	Belin et al. (2015), Ma et al. (2019)	TRIM32, MAX, GSK3B, FBXW7, STAT3
Neurod1 (bHLHa3)	Facilitates axon regeneration.	Lai et al. (2020)	<u>TCF3/E47</u> , <u>EP300</u> , <u>ATOX8</u> , <u>TCF4</u> , <u>TCF12</u> , <u>SIX1</u> , <u>CDK5R2</u> , <u>LHX3</u> , <u>GHRHR</u>
Neurog2 (bHLHa8)	Upregulated after seizures.	Avansini et al. (2018)	<u>ASCL1</u> , <u>TCF3</u> , <u>OLIG2</u> , <u>SIRT1</u>
Npas4 (bHLHe79)	Upregulated after seizures and/or sprouting.	Wang et al. (2014) Lösing et al. (2017)	<u>ARNT</u> , <u>ARNT2</u> , <u>NPAS2</u> , <u>NCOA2</u> , <u>ARNTL</u> , <u>CLOCK</u> , <u>NCOAL1</u> , <u>NCOA3</u> , <u>ARNTL2</u>
Olig2 (bHLHb1)	Upregulated after brain injury.	Buffo et al. (2005)	<u>ID2</u> , <u>ID4</u> , <u>TCF3</u> , <u>SOX8</u> , <u>NEUROG2</u> , <u>SMARCA4</u>
Sharp1 (bHLHe41)	Downregulated after spinal cord hemisection.	Kabos et al. (2002)	<u>BHLHE40</u> , <u>ARNTL/BMALL1</u> , <u>HNF1A</u> , <u>CLOCK</u> , <u>CRY2</u> , <u>GSK3B</u> , <u>CRY1</u> , <u>PER2</u> , <u>BTRC</u> , <u>NPAS2</u>
Sharp2 (bHLHe40)	Downregulated after spinal cord hemisection.	Kabos et al. (2002)	<u>BHLHE41</u> , <u>UBE2I/UBC9</u> , <u>TCF3/E47</u> , <u>ARNTL</u> , <u>NPAS2</u> , <u>CLOCK</u> , <u>FA</u> complex (FANC-E/G/A/F/L/C)

(Continues)

TABLE 2 (Continued)

Gene name	Observation	References	Related genes/molecules based on UniProt and/or STRINGDB
Adult-born neurons			
Ascl1 (bHLHa46)	Associated with adult neurogenesis.	Jessberger et al. (2008)	See above.
Hes1 (bHLHb39)	Associated with adult neurogenesis.	Sueda et al. (2019)	See above.
Hes5 (bHLHb38)	Associated with adult neurogenesis.	Sueda et al. (2019)	See above.
HIF1a (bHLHe78)	Associated with adult neurogenesis.	Matsuda et al. (2012)	See above.
Id2 (bHLHb26)	Associated with adult neurogenesis.	Carrica et al. (2019)	See above.
Neurod1 (bHLHa3)	Associated with adult neurogenesis.	Havrdá et al. (2008)	See above.
Neurog2 (bHLHa8)	Associated with adult neurogenesis.	Gao et al. (2009)	See above.
TCF4 (bHLHe19)	Associated with adult neurogenesis.	Ozen et al. (2007)	See above.
		Shariq et al. (2021)	See above.
			<u>MYOD1</u> , <u>HIVEP2</u> , <u>NEUROD2</u> , <u>BHLHLA9</u> , <u>LDB1</u> , <u>CTNNB1</u> , <u>TLE1</u> , <u>ID1</u> , <u>TCF12</u> , <u>TLE4</u> , <u>MYF5</u> , <u>MYOG</u>
Behaviourally relevant circuit rewiring by adult neurons			
Clock (bHLHe8)	Potentially controls LNv and DN1a rewiring with other clock members.	Petsakou et al. (2015), Ma et al. (2018), Song et al. (2021)	CRY1, CYR2, NPAS2, ARNTL/ BMAL1, ARNTL2/BMAL2, NR3C1, p35, RELA, ID1, ID3, ID2, SIRT1, PRKCA, PER2, BHLHE41
Neurog2 (bHLHa8)	Potentially controls LNv and DN1a rewiring.	Ge et al. (2006), Heng et al. (2008), Pacary et al. (2011), Song et al. (2021)	See above.
Cell transplantation and reprogramming			
Ascl1 (bHLHa46)	Conversion of neurons from other cell types.	Caiazzo et al. (2011), Pang et al. (2011), Torper et al. (2013), Liu et al. (2015), Jorstad et al. (2017), Rivetti di Val Cervo et al. (2017), Karow et al. (2018), Raina et al. (2020), Kempf et al. (2021), Lentini et al. (2021)	See above.
Neurod1 (bHLHa3)	Conversion of neurons from other cell types.	Guo et al. (2014), Pang et al. (2011), Rivetti di Val Cervo et al. (2017), Matsuda et al. (2019), Chen et al. (2020), Puls et al. (2020), Wu et al. (2020)	See above.
Neurod4 (bHLHa4)	Conversion of neurons from other cell types.	Masserdotti et al. (2015) Fukuoaka et al. (2021)	RUNX1T1, TCF3, TCF4, TCF12, FOXN4, <u>TWIST1</u> , <u>TWIST2</u>

(Continues)

TABLE 2 (Continued)

Gene name	Observation	References	Related genes/molecules based on UniProt and/or STRINGDB
Neurog2 (bHLHa8)	Conversion of neurons from other cell types.	Liu et al. (2013), Chouchane et al. (2017), Kempf et al. (2021)	See above.
Id2 (bHLHb26)	Controls granule cell rewiring.	Luo et al. (2021)	See above.

Note: Related genes/molecules are from UniProt or STRING-DB ('active interaction sources': Experiments, database, co-occurrence, co-expression; 'minimum required interaction score': 0.4). bHLH family members are underlined, whereas other factors related to neurogenesis, neural differentiation, axon growth or sprouting are not. Factors not linked to either of these categories and non-bHLH members are not shown.

et al., 2021) (Figure 3a and Table 2). In addition, Clock may directly stabilize RhoA, as shown in cancer cells (Ma et al., 2018). Neurog2 and Ascl1, which are frequently used to reprogram different types of cells into neurons (Table 2), have been shown to induce the expression of Rnd2 and Rnd3 respectively (Ge et al., 2006; Heng et al., 2008; Pacary et al., 2011). Since both Rnd2 and Rnd3 promote RhoA inactivation, Neurog2 and Ascl1 likely create cell states with increased capacity for axon elongation (Figure 3b). And finally, (iv) bHLH factors play a key role in achieving successful cell conversion during grafting and reprogramming (Caiazzo et al., 2011; Chen et al., 2020; Chouchane et al., 2017; di Val et al., 2017; Fukuoka et al., 2021; Guo et al., 2014; Jorstad et al., 2017; Karow et al., 2018; Kempf et al., 2021; Lentini et al., 2021; Liu et al., 2013, 2015; Masserdotti et al., 2015; Matsuda et al., 2019; Pang et al., 2011; Puls et al., 2020; Raina et al., 2020; Torper et al., 2013; Wu et al., 2020) (Table 2). Further, bHLH family members control the expression of several other molecules that were identified to affect wiring (e.g., Adcy1, Slit1, Stat3, and Tle1, expression of which was changed by Id2 overexpression) (Luo et al., 2021), and bHLH factors have been also associated with other, non bHLH molecules related to neurogenesis, neural differentiation, axon growth or sprouting (Table 2).

Despite these observations, delineating the role of bHLH and other transcriptional regulators in the wiring process remains challenging. At least in adult-born and reprogrammed neurons this would require experiments that probe wiring but do not affect other domains of cellular maturation. Another difficulty is that members of the bHLH family regulate both the expression and activity of each other (Baker & Brown, 2018; Cho et al., 2007; Dennis et al., 2019; Imayoshi & Kageyama, 2014). To overcome challenges in this domain of research, cell type-specific expression and molecular interaction maps of transcription factors will likely be helpful.

3.2 | Axon elongation in established circuits

In apparent contradiction to models that posit broad growth inhibition after development, the above-mentioned examples of adult-brain circuit formation clearly demonstrate robust axon elongation in already established circuits. While clearly an important issue, there is still too much uncertainty with regard to cellular mechanisms that allow elongating axons to bypass presumed inhibitory signals in the adult brain. Growth inhibition is thought to be rendered by a specialized signalling system that is comprised of growth inhibitory

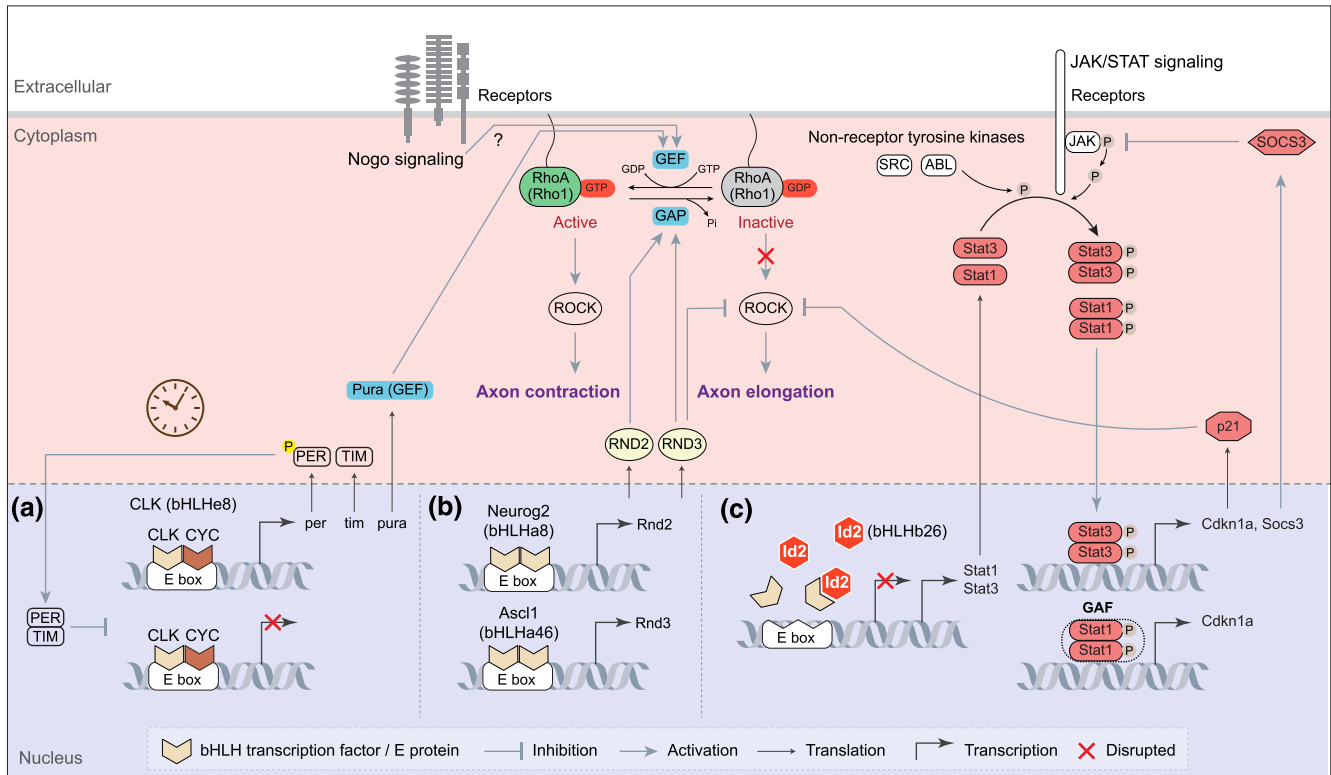


FIGURE 3 bHLH-dependent mechanisms and adult-brain circuit formation. Here, we highlight potential mechanisms by which bHLH transcription factors and regulators may support circuit formation in adult brain. (a) The bHLH factor Clock (CLK) and Cycle (CYC) are presumed to drive Pura (a Rho1 GEF) expression in a circadian manner. Pura promotes activation of Rho1 (RhoA in mammals), which is a key regulator of daily periodic rewiring of *Drosophila* LNV and DN1a neurons. See Petsakou et al. (2015) and Song et al. (2021). (b) The bHLH factors Neurog2 and Ascl1 are frequently used to reprogram different type of cells into neurons. Among other genes, Neurog2 and Ascl1 promote expression of Rnd2 and Rnd3 respectively. Rnd2 and Rnd3 can inactivate RhoA, and independently of its effect on RhoA, Rnd3 can also inhibit ROCK, allowing axon elongation. As a potential mechanism, Rnd2- and Rnd3-mediated ROCK inactivation may facilitate circuit formation by newly engineered neurons. Although independently of cell reprogramming, the overexpression of Ascl1 in rat brainstem neurons has been shown to facilitate noradrenergic axon regeneration after spinal cord injury. See Heng et al. (2008), Pacary et al. (2011), Williams et al. (2015), and Table 2. (c) Overexpression of Id2 induces axonal wiring in developing, injured, and healthy adult neurons. In healthy adult neurons (hippocampal granule cells), Id2 overexpression leads to upregulation of Stat1, Stat3, Cdkn1a, and Socs3. Most likely the upregulation of Cdkn1a and Socs3 is a consequence of increased Stat3 and/or Stat1 activity. Stat3 itself has been shown to facilitate axon regeneration after neuronal injury. p21 (protein name of Cdkn1a) is a ROCK inhibitor and potentially a key mediator of axon elongation after Id2 overexpression. By contrast, upregulation of Socs3, an inhibitor of Stat protein phosphorylation, and thus activity, may support a control mechanism that balances (negatively regulates) axon growth after Id2 overexpression. See Chin et al. (1996), Bareyre et al. (2011), Smith et al. (2011), Sun et al. (2011), Pernet et al. (2013), and Luo et al. (2021).

receptors/complexes on axons (e.g., NogoR/RTN4R, Lingo1, Troy, PirB) and myelin-associated growth inhibitory ligands in the surrounding tissue (e.g., Nogo, MAG, and OMgp). This model is extensively supported by neuronal culture and nerve injury studies, in which application of ligands inhibited axon growth or neutralization of ligands and/or receptors enhanced axon growth (Fujita & Yamashita, 2014; Schwab, 2010; Yiu & He, 2006). By extension, it has been hypothesized that myelin-associated growth inhibitors are physiologically relevant for stabilizing neural circuitry, and act as a tonic negative regulator of growth in the healthy adult nervous system (Schwab, 2010; Yiu & He, 2006). Although this

hypothesis has yet to be conclusively proven, many studies show that components of the signalling system can restrict synapse formation and different forms of experience-dependent synaptic and circuit plasticity (Baldwin & Giger, 2015; Delekate et al., 2011; Guzik-Kornacka et al., 2016; Iobbi et al., 2017; Kellner et al., 2016; Lee et al., 2008; McGee et al., 2005; Raiker et al., 2010; Petrinovic et al., 2013; Stehle et al., 2021; Stephany et al., 2014; Syken et al., 2006; Wills et al., 2012; Zagrebelsky et al., 2017; Zemmar et al., 2018). Intracellularly, the RhoA/ROCK pathway has been implicated as a key signal transducer for these growth inhibitors, in part because of its ability to induce cytoskeletal reorganization,

such as growth cone collapse, that disadvantages further growth (Fujita & Yamashita, 2014; Schwab, 2010; Yiu & He, 2006). Here, we highlight evidence that links bHLH factors to the regulation of Nogo/RTN4 receptors and intracellular transducers, which are possible sites for the disinhibition of axon growth in adult brain.

First, the developmentally regulated degradation of Id2 was found to correlate with upregulation of the protein form of Nogo/RTN4 receptors (Lasorella et al., 2006). Although the reciprocal thesis, that is, if surface expression of Nogo/RTN4 receptors is down-regulated in response to Id2 upregulation, has not been tested, the lack of inhibitory receptors could feasibly help growing axons to evade inhibitory signals. However, at least during Id2-induced mossy fibre sprouting, the mRNA levels of Nogo/RTN4 receptors did not change (Luo et al., 2021). Further, independently of Id2, grafting studies in which this issue was investigated have reported powerful axon growth despite continued expression of Nogo/RTN4 receptors (Lu et al., 2012; Steinbeck et al., 2012). In addition, a more recent study highlighted that apart from mediating growth inhibition, Nogo/RTN4 receptors play another role during circuit formation (Wang, Miao, et al., 2021). Specifically, this study identified the synaptogenic BAI adhesion GPCRs as high affinity binding ligands for Nogo/RTN4 receptors and showed that while this binding still inhibited axon growth, it was also required for synapse formation. By extension, temporally controlled surface presentation of Nogo/RTN4 receptors on the elongating fibres may be necessary, rather than adverse, for adult-brain formation of synaptic circuits.

Second, with regard to downstream effectors, bHLH factors may exert control over the RhoA/ROCK pathway independently of Nogo/RTN4 signalling. As discussed above, Clock likely controls periodic rewiring of *Drosophila* circuits through Rho1 (RhoA in mammals), and Neurog2 and Ascl1 feasibly inactivate RhoA/ROCK to allow axon elongation in reprogrammed neurons. In addition to these, other observations support a link between bHLH factors and RhoA/ROCK. As shown in developing neuronal cultures, Id2 overexpression promoted axon growth through upregulation of Neurog2 (Huang et al., 2019). While knockdown of Neurog2 impaired axon growth in this model, demonstrating the necessity for Neurog2, Neurog2 overexpression alone was not sufficient for axon growth because this manipulation only induced indistinguishable neurite growth from the cells (Huang et al., 2019). Thus, axon specification and/or growth in these cells required both Id2 and Neurog2. By contrast, in adult GCs, Id2 overexpression promoted mossy fibre rewiring without upregulating Neurog2 (Luo et al., 2021), which is normally not expressed by this cell

type. However, in GCs, but not in developing neuronal cultures (Huang et al., 2019), Id2 increased the expression of Cdkn1a (Luo et al., 2021), the protein product of which (called p21 or Cip1/WAF1) is a potent ROCK inhibitor (Tanaka et al., 2002) and was shown to facilitate axon growth (Tanaka et al., 2004) (Figure 3c). Together, these observations suggest that Id2 may support axon growth through RhoA/ROCK inhibition by activating Neurog2 or Cdkn1a. Further, in adult GCs, Id2 overexpression upregulated Stat1 and Stat3. Stat3 has been previously implicated in promoting axon growth after neuronal injury (Bareyre et al., 2011; Pernet et al., 2013; Sun et al., 2011), and both Stat1 and Stat3 were shown to promote Cdkn1a expression (Chin et al., 1996; Pernet et al., 2013; Smith et al., 2011). Thus, it is likely that Cdkn1a expression was a consequence of Id2-induced Stat1 and/or Stat3 upregulation. While bHLH-mediated RhoA/ROCK inhibition represent a feasible mechanism for allowing axon elongation, future studies will need to confirm if Id2-, Neurog2-, and Ascl1-induced RhoA/ROCK inhibitors are indeed translated and contribute adult-brain circuit formation.

Third, independently of the role of Id2 in transcriptional regulation, this molecule has been shown to promote growth cone formation and stabilization in developing neurons (Ko et al., 2016). Potentially, such a mechanism could also help to overcome growth inhibition in adults. However, expression of a mutant form of Id2, which was used to prevent growth cone formation in developing neurons (Ko et al., 2016), still induced mossy fibre rewiring in adult GCs (Luo et al., 2021). Nonetheless, it remains possible that Id2-mediated growth cone stabilization supports axon growth in other cell types in the adult brain, for example, in adult-born, grafted, and reprogrammed neurons, which are immature in the beginning. More broadly, the question of whether growth cone formation by adult neurons is similar to that during development remains open.

Together, rather than providing solutions, these observations serve as conceptual access points to the conundrum of axon elongation in adult circuits. They also underscore the importance of clarifying the role of growth inhibitory signals and receptors in adult-brain circuit formation.

3.3 | Target specificity and synapse formation

Perhaps target specification appears to be the most susceptible to modifications in adults. The different circuits formed by hippocampal mossy fibres highlight this. The developmental pattern is well characterized: mossy fibres

originate from GCs and project into hilus and CA3 (Blaabjerg & Zimmer, 2007; Hainmueller & Bartos, 2020). As described above, adult-born GCs precisely replicate this pattern. However, during mossy fibre sprouting GCs make new projections into the inner molecular layer of dentate gyrus (Laurberg & Zimmer, 1981; Luo et al., 2021; Sutula et al., 1988; Tauck & Nadler, 1985; Wenzel et al., 2000). Although adult-born GCs demonstrate that axon growth into CA3 would be permitted, sprouting mossy fibres do not opt for this. The opposite also holds true. Adult-born GCs do not normally grow axons into the inner molecular layer (Briones et al., 2021; Drew et al., 2016; Faulkner et al., 2008; Markakis & Gage, 1999; Restivo et al., 2015; Sun et al., 2013; Temprana et al., 2015; Toni et al., 2008; Trincherro et al., 2019; Zhao et al., 2006). The most likely explanation for this, based on what we know about development, is that adult-born GCs and sprouting adult GCs utilize different sets of cell-surface molecules for axon guidance. This may be because sprouting induction methods do not recruit all developmentally relevant molecules in mature neurons, but potentially others that specify different targets. In addition to GCs, circuits formed by several other adult neuronal cell types (e.g., sprouting CA1, CA3, and cortical pyramidal neurons) display atypical targeting that is different from their developmentally established profiles (see Section 2.1). In these cases, it is also possible that although developmentally relevant molecules are recruited (or remain expressed), but complementary binding partners are not anymore present in the original target-cell population after development. Given that adult-born and grafted/reprogrammed neurons, which proceed through all steps of cell development, frequently recapitulate developmental patterns and that neurons which periodically rewire naturally do this, an altered display of guidance and/or target recognition receptors on sprouting axons is a likely factor in most cases when atypical connections are formed. Results from studies that employed heterotopic transplants provide further support for this scenario.

As discussed above, homotopic transplantation of embryonic motor cortical cells into motor cortex resulted in projections appropriate for motor cortical neurons (Gaillard et al., 2007). In the same study, transplantation of embryonic visual cortex cells into the motor cortex (heterotopic transplant) was also tested. However, axon projections formed by homotopic and heterotopic transplants were different. After heterotopic transplantation, new projections grew into visual cortical areas and caudate putamen, appropriate for visual cortical but not for motor cortical neurons. As also discussed, homotopic transplantation of embryonic mesencephalic cells reconstituted the nigrostriatal pathway (Gaillard et al., 2009; Thompson

et al., 2009). In their study, Gaillard et al. (2009) tested embryonic olfactory bulb cells as heterotopic transplant, because adult olfactory areas also contain dopaminergic neurons, the cell type of interest for this study. Although dopaminergic neurons appeared in the graft, growing fibres remained in close proximity of the graft and never reached the striatum. Thus, already committed embryonic cells appear to give rise to neurons, whose projection specificity is predetermined—most likely by the availability of guidance receptors on their axons.

Another important question is whether new circuits formed by elongating axons need to compete with already established ones. Such competition could take place already at the level of synapse formation, which has been viewed to principally occur during development (Katz & Shatz, 1996; Squire et al., 2012). This question has been investigated also in the context of hippocampal GCs. In 2–6 months old mice, electron microscopy images in the CA3 area demonstrated that adult-born GCs formed synapses at sites already contacted by other presynaptic terminals (Toni et al., 2008; Toni & Sultan, 2011). New synapse formation on pre-existing postsynaptic targets would indicate synaptic competition. Although in juvenile mice, functional analysis in which the activity of GCs was permanently silenced from early postnatal stages supported this hypothesis. Axonal projections by silenced GCs first developed normally, but they retracted by 3–4 weeks of age (Yasuda et al., 2011). The retraction was dependent on ongoing neurogenesis, and driven by activity-dependent competition between mature and newborn GCs, which were not silenced (Yasuda et al., 2011). Another study performed a similar experiment but in adult mice. This study employed an inducible technique for long-term and reversible silencing in already matured GCs (Lopez et al., 2012). During silencing, existing GCs synapses were presumed to suffer a competitive disadvantage if active synapses formed by adult-born GCs (born after silencing and themselves are not silenced) were preferred by postsynaptic neurons. However, reversal of 3–6 months of silencing revealed that existing axons were not retracted, nor were their synaptic transmission affected. While this result suggests that synaptic competition may not be prevalent during adult-brain circuit formation, it is also possible that relative contribution of adult-born GC axons to the entire GC axon population was too small at this age to induce gross axon retraction as seen at younger age (Lopez et al., 2012). Thus, more detailed analyses will be necessary to establish if the adult brain has capacity to host circuits in addition to those established during development, or only at the expense of those.

Although region- and cell type-specificity is clearly recognizable in several forms of adult-brain circuit formation,

it remains unclear how elongating axons are guided through already established circuits and to specific target neuron type(s) while rejecting other options. Adaptation of cutting-edge in vivo time-lapse imaging, such as dynamic morphometrics (Hogg et al., 2021), and intravital (Falkner et al., 2016; Pilz et al., 2018) and whole-brain imaging (Li et al., 2021), will likely make important contributions to answering those questions. For example, time-lapse imaging has the capacity to reveal spatial location of key decision points, where elongating fibres may or may not immediately find their final path. Moreover, time-lapse imaging over longer periods would enable to study long-term stability of newly formed circuits. Together with results of molecular analyses, such information could facilitate gaining control over the selection of target cell types, a potential prerequisite for re-establishing damaged circuits after injuries and in disorders.

4 | CONCLUDING REMARKS

In summary, evidence supports that neurons have the capacity to form new circuits in adult brain. Some of the circuit formation are ongoing and their relevance to behaviour and memory already warrants an increased attention for understanding their mechanisms. Since detection of such ongoing wiring events was made possible only through specific experiments that were designed to probe them, it remains possible that further behaviourally relevant circuit rewiring exists, which itself is an exciting area for future research. Furthermore, disease modelling represents another area of research where the studying of adult-brain wiring has clear benefits. Multiple disorders have been associated with atypical wiring but without a clearly established role of new circuits in disease pathology. This may be because other cellular or circuit pathologies often create a complex landscape, in which dissociation of causes and consequences is difficult. In these cases, cell-autonomous induction of particular wiring events are especially useful. Additionally, studying of circuit formation in adult brain could lead to a deeper understanding of principles behind the brain's connectivity. Currently, the lack of this understanding represents not only an academic challenge but effectively hinders successful repair after damage. An eventual ability to induce and control target-specific wiring in adult circuits would be a major step towards achieving these goals.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

There were no new data generated for this study.

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